

REMARKS

Reconsideration and withdrawal of the objection to the specification and rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1, 30 and 70 are amended. The amendments are intended to advance the application and are not intended to concede the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the present application. Claims 1-84 are pending.

The specification is amended to indicate trademarks.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claims 1-14 were rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the detection of multiple enzymes in genetically modified murine cells, allegedly does not reasonably provide enablement for all species of possible prokaryotic and eukaryotic organisms which may or may not have been transfected or genetically modified and lysates of prokaryotic and eukaryotic cells. This rejection is respectfully traversed.

The art of detecting enzymes is well-developed, whether those enzymes are purified, in lysates or in whole cells, for both prokaryotic and eukaryotic cells. See, for instance, U.S. Patent No. 6,586,196, and Mandlekar et al. (Cancer Res., 60:5995 (2000)), references cited against the claims under 35 U.S.C. § 103; Technical Bulletin for CytoTOX-ONE™ (of record); Lui et al., Luminescence, 15:45 (2000) (of record); Nolkrantz et al., Anal. Chem., 74:4300 (2002) (of record); and Qazi et al., Luminescence, 17:106 (2002) (of record). Given the Examiner's acknowledgement that the level of skill in the art is high (Wands factor 6) and the predictability regarding enzymes and substrates is high (Wands factor 7), in view of Applicant's numerous working examples and detailed direction and guidance (Wands factors 2 and 3), it would not require undue experimentation to practice the entire scope of Applicant's invention.

Therefore, withdrawal of the "enablement" rejection under 35 U.S.C. § 112(1) is respectfully requested.

Claims 1-14 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner asserts that the specification

does not teach the measurement of a quantifiable amount of enzyme, substrate or co-factor. This rejection is respectfully traversed.

The Examiner is respectfully requested to consider Figures 7A, 7C, 8A, 8C, 9A, 9B, 9C, 9D, 10B and 10D in Applicant's specification, which plots relative luminescence or fluorescence versus increasing concentrations (e.g., U/mL or μ M) of particular enzymes or co-factors. It is well known that, based on a standard curve, the amount of enzyme or other molecule in a test sample may be calculated. Applicant need not teach what is well known to the art.

Accordingly, withdrawal of the "written description" rejection under 35 U.S.C. § 112(1) is respectfully requested.

The 35 U.S.C. § 112, Second Paragraph, Rejection

Claim 1 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The amendment to claim 1 to recite "a first enzyme" and "a second enzyme" obviates the § 112(2) rejection. Thus, withdrawal of the § 112(2) rejection is respectfully requested.

The 35 U.S.C. § 102 Rejection

Claims 1 and 4-5 were rejected under 35 U.S.C. § 102(b) as being anticipated by Bronstein et al. (U.S. Patent No. 6,586,196 B1). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

The Examiner is requested to note that the present application was filed on January 22, 2004. Therefore, Bronstein et al., which issued on July 1, 2003 and claims the benefit of the filing date of December 15, 1998, is § 102(a) or § 102(e), not § 102(b), prior art.

Bronstein et al. disclose a method to measure the activity of multiple enzymes, where at least one enzyme is endogenous and at least one enzyme is capable of reacting with a dioxetane (yielding chemiluminescence) (column 3, line 65-column 4, line 5), or where the enzymes are selected from the group consisting of reporter enzymes and endogenous enzymes, where at least one enzyme is an endogenous enzyme (claims 1, 27 and 28). Preferred reporter enzymes are

disclosed as luciferase, β -galactosidase (β -gal), glucuronidase, alkaline phosphatase, carboxyl esterase, acid phosphatase and glucosidase (column 6, line 65-column 7, line 1).

The Examples in Bronstein et al. describe the detection of alkaline phosphatase and luciferase with a reagent having a 1,2-dioxetane substrate for alkaline phosphatase and luciferase detection reagents in a sequential assay; β -gal and alkaline phosphatase with a dioxetane containing β -gal substrate and a dioxetane containing alkaline phosphatase substrate in a sequential assay; β -gal, luciferase and alkaline phosphatase with a dioxetane containing β -gal substrate, luciferase detection reagents and a dioxetane containing alkaline phosphatase substrate in a sequential assay; β -glucosidase and luciferase with a dioxetane containing β -glucosidase substrate and luciferin in a sequential assay; and PLAP and β -glucosidase with a dioxetane containing PLAP substrate and a dioxetane containing β -glucosidase substrate in a sequential assay. No assays which detect fluorogenic and luminogenic products are disclosed in Bronstein et al.

Therefore, withdrawal of the 35 U.S.C. § 102 rejection over Bronstein et al. is respectfully requested.

The 35 U.S.C. § 103 Rejection

Claims 1-14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Bronstein et al. (U.S. Patent No. 6,586,196 B1) in view of Mandlekar et al. (Cancer Res., 60:5995 (2000)). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Mandlekar et al. report that tamoxifen induces the activity of caspase-3-like proteases in ER-negative breast cancer cell lines, as evidenced by the cleavage of a fluorogenic tetrapeptide substrate and a polyADP-ribose polymerase (abstract). Caspases were detected using fluorogenic substrates for caspase-1, -3, -6 and -8, substrates which had methylcoumaryl-7-amide (MCA), and for caspase-9, a substrate which had trifluoromethylcoumaryl-7-amide (FCA) (page 5996; Figure 3). After cleavage by the appropriate caspase, those substrates yield the fluorophores aminoemethylcoumarin (AMC) and aminotrifluoromethylcoumarin (AFC), respectively. The assays to detect those caspases were apparently run in parallel.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the teachings of Bronstein et al. and Mandlekar et al. because it would simplify the method taught by Bronstein et al. making it more efficient, that one of ordinary skill in the art would have been motivated to combine luminogenic and fluorescent assays because the step of inactivating the first enzyme could be omitted, and that one of skill in the art would have a reasonable expectation of success in combining the two methods.

Disparate enzyme kinetics, assay chemistries and incubation requirements of various reporter enzymes can complicate combining two reporter enzymes into an integrated, single tube or dual reporter assay format. Notably, neither Bronstein et al. nor Mandlekar et al. disclose or suggest multiplex luminogenic and fluorogenic assays for enzyme-mediated reactions. Moreover, multiplex luminogenic assays (see, for example, U.S. Patent No. 5,744,320) and multiplex fluorogenic assays (see, for instance, Nolkrantz et al., *Anal. Chem.*, 7:4300 (2002)) were known to the art before Applicant's filing. It is only Applicant's specification that provides the reasonable expectation that luminogenic and fluorogenic multiplex assays for enzymatic reactions can be combined.

Accordingly, withdrawal of the § 103 rejection is respectfully requested.

Information Disclosure Statement

Applicant submitted a Supplemental Information Disclosure Statement and a 1449 Form on February 24, 2006. Applicant respectfully requests that an initialed copy of the 1449 Form be returned to Applicant's Representatives to indicate that the cited references have been considered by the Examiner.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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By their Representatives,

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Date

JUN 21, 2006

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 21 day of June, 2006.

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